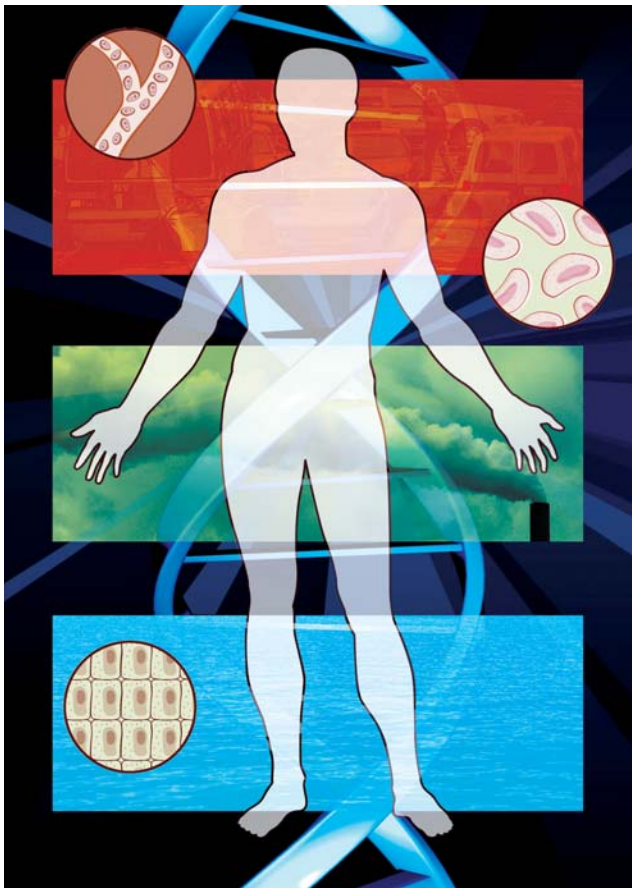
Gene–Environment Studies: Who, How, When, and Where?

With the sequencing of the human genome completed, the question becomes: what now? Many common diseases are known to be associated with genetic variants, or changes in single nucleotides of the DNA making up the human genome. However, scientists still have many questions about how individual gene variants, and interactions between variants and environmental factors, contribute to an individual's risk of developing common diseases such as cancer, obesity, and heart disease.

Some scientists believe the only way to answer those questions is through a large prospective cohort study, collecting DNA samples and information about exposure to a variety of environmental factors from 500,000 to 1 million participants and following this random sampling of the population over a number of years. But such a study would require a huge investment of time, effort, and money; the DHHS Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) estimates the cost at roughly $3 billion, possibly more. In addition, such an endeavor would likely raise significant social, legal, and ethical issues concerning privacy, consent, public involvement, and communication.

Now a new draft report by the SACGHS examines the policy issues related to such a study. The report concludes that, although conducting a large prospective study presents major challenges, it also has the potential to result in significant health benefits.



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Examining the Angles

In 2004 the SACGHS decided to address the question of whether the United States should undertake a large cohort study in this country. The committee formed the Large Population Studies Task Force to dig into the issues that would be involved in such a study. Since a large population project could potentially have significant ethical, regulatory, scientific, and public health implications, NIH director Elias A. Zerhouni asked the committee to focus its inquiry on the associated policy issues.

Through consultation with experts in the field, fact-finding research, and deliberation, the committee identified several specific policy issues. In May 2006, the committee issued a draft report (available at http://www4.od.nih.gov/oba/SACGHS/public_comments.htm) that discussed these key policy issues and made recommendations for how they might be addressed. The report was then opened to the public for comment through the end of July 2006.

The report devotes an entire chapter to the need for public involvement in all stages of the decision making, planning, and execution of such a study. Suggested populations to consult include the scientific and international communities, representatives of populations that might be involved in the research, health care providers and their institutions, and those who volunteer to participate in the project as research subjects. The report also stresses the need to include in the study populations who are underinsured or who are underserved by the health care system. Since such a study would require a large investment of public money, states the report, it is only reasonable and fair that the benefits should be equitably distributed among the population.

Honing the Tools

The report notes that some scientists raise the question of whether scientific methods to determine gene–environment interactions are mature enough to obtain maximum value from a large prospective study. Current methods of measuring exposures allow scientists to determine that an environmental exposure is correlated with disease, but it is still difficult to understand the mechanisms underlying such associations, said NIEHS director David Schwartz during a June 2006 presentation to the SACGHS.

Schwartz is co-chairman, with National Human Genome Research Institute director Francis Collins, of the NIH Coordinating Committee for the Genes and Environment Initiative, a just-launched research effort that aims to develop more precise tools that could be useful in a large cohort study. Tools such as biological sensors and biomarkers would allow scientists to determine not just what a person has been exposed to, but whether the person's body is responding to an exposure, Schwartz said during his presentation.

Other concerns focus on issues of study design. John Hewitt, director of the Institute for Behavioral Genetics and a professor of psychology at the University of Colorado, also made a presentation before the SACGHS in June 2006. Hewitt suggested that the committee consider highlighting the need for a smaller substudy of identical twins, which could serve to confirm apparent associations between disease and either environmental factors or gene–environment interactions.

"The big concern is that a large-scale national study has a very wide geographic and demographic range, so it's very difficult to sort out what are truly environmental differences and what are truly genetic differences," Hewitt says. "When you study genetically identical pairs, you know that the environmental differences within that pair aren't correlated with genetic differences, because there are [no genetic differences]."

A substudy of twins may also help keep the larger study honest. "You could certainly take things that appear to be interesting in the large study and get an immediate check [in a twin study] on whether those environmental associations held up when you controlled for the genotype," Hewitt says.

How and When to Return Results

Richard Sharp, an assistant professor of medicine with the Center for Medical Ethics and Health Policy at Baylor College of Medicine, praises the report's commitment to reaching out to the public and to underrepresented communities. But he expresses surprise that the report didn't pay more attention to what he calls "relatively obvious" ethical issues surrounding informed consent and communicating research results to participants.

"If you're a patient in a clinic in a hospital, and someone comes up to you and says 'we want to enroll you in this twenty-year study,' or however long it ends up being, what would you need to know before you felt like you could say yes or no?" Sharp asks. He and NIEHS health administrator Pat Chulada conducted a study with participants in the NIEHS's Environmental Polymorphisms Registry to answer these questions. The data from that study are now being analyzed.

Sharp also stresses the importance of establishing a process for communicating research results to participants. For instance, if certain genes are found to greatly increase risk for certain diseases, should study participants be informed about these results and their genetic status? If so, when and how? The report suggests that any large prospective study should include a standing committee to address such ethical issues but doesn't outline a specific process for returning results. "We don't really know what to do in terms of returning results of unclear value," Sharp says.

Task force chairman Huntington F. Willard, director of the Institute for Genome Sciences & Policy at Duke University, emphasizes that the draft report has not yet been approved by the full committee. With the comment period now completed, the task force will consider the comments, modify the draft, and present it to the SACGHS for its consideration and action, most likely at the committee's November 2006 meeting. However, even as many scientists express enthusiasm for the benefits of such a study, the SACGHS and others will still need to explore the many other challenges to be addressed, not the least of which is the uncertain availability of funding. **–Angela Spivey**

Student Action with Farmworkers/NC Department of Labor

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NIEHS-Supported Research

Inadequate Housing May Put Immigrant Farmworkers at Risk

Early J, Davis SW, Quandt SA, Rao P, Snively BM, Arcury TA. 2006. Housing characteristics of farmworker families in North Carolina. J Immigr Minor Health 8(2):173–184.

Even though rates of substandard housing for the general U.S. population are relatively low, percentages for subpopulations such as immigrants are disproportionately high. In this report NIEHS grantee Thomas A. Arcury and colleagues at Wake Forest University School of Medicine describe specific housing conditions for immigrant farmworker families in North Carolina, and identify housing features that leave the occupants vulnerable to environmental exposures.

Inadequate housing is a known contributor to poor health. Overcrowding and lack of proper sanitary facilities can lead to higher incidences of infectious disease, and substandard housing with structural or electrical problems poses the danger of physical injuries and exposure to toxic substances such as lead and polychlorinated biphenyls. Inadequate housing can also have negative effects on psychological health.

The researchers analyzed data from four surveys of North Carolina farmworker communities conducted in 2001 and 2003 by specially trained interviewers fluent in Spanish. From the survey responses, the researchers documented housing conditions for 234 households of immigrant Latino farmworkers, most of whom (90%) had immigrated from Mexico. All participating houses had at least one adult farmworker and one child. The investigators considered three main features in the participants' houses that could affect their health: characteristics of the dwelling itself, characteristics of the people comprising the household, and housekeeping behaviors.

Compared to 7% of the U.S. population as a whole, 54–70% of the immigrants surveyed lived in mobile homes, and many (36–46%) lived in crowded conditions. Most of the homes had only one bathroom. Most respondents did not own their own dwellings, and therefore had no control over how often necessary repairs were addressed.

Many respondents reported living in households that included more than the traditional nuclear family (two adult parents and children). Most reported that they dusted, swept, and mopped their floors daily. Many did not own a working vacuum cleaner, and cleaned carpets with water or brooms. Over a third of respondents did not have a working clothes washer or dryer in the home, and up to 44% lived adjacent to agricultural fields; both conditions potentially left them susceptible to pesticide exposure.

The authors conclude that the health of these families may be at risk due to inadequate housing. They add that research focusing on farmworker perceptions and decisions regarding their housing situations as well as more information on housing availability, affordability, and quality is needed. **–Tanya Tillett**

BEYOND THE BENCH

Flagging Environmental Health Awareness on Beaches

During the summer months, folks flock to the beach to enjoy the combined pleasures of sun and sea. Smart beachgoers know that before they take a dip, they should check whether any warning flags are flying, indicating hazardous conditions such as rip currents or the presence of jellyfish. Now, Galveston swimmers can look for a new "environmental alert" flag. The new flag warns beachgoers of air and weather conditions that could pose a health threat, especially to particularly vulnerable populations such as asthmatics, the elderly, and people with heart or lung disease.

The new flag reflects the translation of research findings into concrete community health education by investigators in the Asthma Pathogenesis Core of the University of Texas Medical Branch (UTMB) and codirectors of the Asthma Community Outreach and Education Core (COEC), in partnership with the Galveston Sheriff's Office Beach Patrol, the Galveston Park Board of Trustees, and the Texas Commission on Environmental Quality.

For better beachgoing. A new orange flag indicates when Galveston beaches are experiencing poor air quality conditions that might affect vulnerable populations.

Three years ago, investigators Sharon A. Petronella and Edward G. Brooks initiated the Gulf Coast Study of Urban Air Quality and Respiratory Function (GC SURF) to study pulmonary function in a cohort of lifeguards in Galveston. During the summers of 2003 through 2005 they collected pulmonary effects data on the GC SURF cohort by using portable spirometers, which measure the amount of inhaled and exhaled air. This allowed them to evaluate exposure to and effects of air pollutants and weather conditions including nitric oxide, nitrogen dioxide, ozone, particulate matter, wind speed, outdoor temperature, relative humidity, and solar radiation.

The data gathered helped the investigators determine particular times of day when changes in air quality could affect breathing health. Now, whenever the Texas Commission on Environmental Quality deems that air quality conditions exist that might affect vulnerable populations, the city's 26 lifeguard towers and 7 freestanding beach stations deploy an orange flag and display information on posters and in brochures describing the particular environmental issues and guidelines for protecting health.

The program, which the COEC believes to be the first in the nation to enlist lifeguard participation in an environmental health public warning system, provides educational materials on ozone, fine particulates, and, as needed, red tide. The group has now also developed a partnership with the Galveston County Health District to display the environmental flags at each tower when water quality is less than optimal.

Petronella says the alert program is the result of a true collaborative effort between the partner organizations and is a solid indication of what can happen when a community comes together. The developers, who hope the orange flag alert program can be used as a model for other beaches, presented it at the annual meeting of the U.S. Lifesaving Association in Galveston in 2004.

In addition to the GC SURF flag alert program, the Asthma Pathogenesis Core of the UTMB COEC is also involved in other projects that focus on building connections between research, education, and community health. One of these, the Texas Emergency Department Asthma Surveillance Project, is a collaborative effort coordinated by Charles Macias of Baylor College of Medicine that links the databases of Baylor and three other Texas hospitals to track asthma-related emergency room visits. The results will aid in the development of an educational intervention program. Another project, Communities Organized Against Asthma and Lead, is an environmental justice consortium combining the educational outreach efforts of the COEC with community social services and health care providers. COEC investigators are also involved in a school asthma surveillance project.

"As researchers involved in the UTMB NIEHS Center Asthma Pathogenesis Core, we work in and with our community to identify problems and potential solutions related to our environment," says Petronella. "Our COEC, however, allows us to take our work one crucial step further—by actually assisting the community with education, intervention, and development of policies that will effect positive change in the health of our residents and all visitors to our part of the Gulf Coast."

In essence, Petronella says, the COEC forms the bridge from basic science to the public. "This is essential to our success," she adds, "since the key to any public health research program is the use to which the data are put." **–Tanya Tillett**

Top to bottom: Chad Greene/*Galveston County Daily News*; Gloria-Leigh/iStockphoto